The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 27

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DENNIS E. HALLAHAN, RALPH R. WEICHSELBAUM, DONALD W. KUFE, GREGORY S. SIBLEY, and BERNARD ROIZMAN

Appeal No. 1999-1222
Application No. 08/540,343

ON BRIEF[1]

Before ROBINSON, ADAMS, and MILLS, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

VACATUR and REMAND TO THE EXAMINER

On consideration of the record we find this case is not in condition for a decision on appeal. For the reasons that follow, we vacate[2] the pending rejection under 35 U.S.C. § 112, first paragraph, and remand the application to the examiner to consider the following issues and to take appropriate action.

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[1] In response to appellants' request (Paper No. 20, received June 19, 1998) an oral hearing was scheduled for 1:00 pm on July 26, 2001 (Paper No. 23, mailed May 22, 2001). We note appellants' confirmed their attendance (Paper No. 24, received June 11, 2001). The Merits Panel convened at 1:00 on July 26, 2001 to hear appellants' oral argument. However, appellants failed to attend the oral hearing. Accordingly, this appeal was considered on Brief.

[2] Lest there be any misunderstanding, the term "vacate" in this context means to set aside or to void. When the Board vacates an examiner's rejection, the rejection is set aside and no longer exists.

Claims 13, 18, 23, 40, 41 and 46 are illustrative of the subject matter on appeal and are reproduced below:

13. A method of inhibiting growth of a tumor in vivo comprising delivering to said tumor, in combination, a herpes simplex virus and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

18. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a herpes simplex virus and (ii) ionizing radiation, wherein the combination of herpes simplex virus infection and radiation is more effective than ionizing radiation alone.

23. A method of killing a tumor cell comprising the steps of:
(a) contacting said tumor cell with a herpes simplex virus; and
(b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said herpes simplex virus.

40. A method of inhibiting growth of a tumor in vivo comprising delivering to said tumor, in combination, an adenovirus lacking an exogenous therapeutic gene and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

41. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a [sic] adenovirus lacking an exogenous therapeutic gene and (ii) ionizing radiation, wherein the combination of adenovirus infection and radiation is more effective than ionizing radiation alone.

46. A method of killing a tumor cell comprising the steps of:
(a) contacting said tumor cell with an adenovirus lacking an exogenous therapeutic gene; and
(b) exposing said cell to a does of ionizing radiation sufficient to kill said cell in conjunction with said adenovirus.

The references relied upon by the examiner are:

Dorudi et al. (Dorudi), "Gene transfer therapy in cancer," Br. J. Surg., Vol. 80, pp. 566-572 (1993)

Culver et al. (Culver), "Gene therapy for cancer," Trends in Genetics, Vol. 10, No. 5, pp. 174-178 (1994)

Hodgson, "Advances in vector systems for gene therapy," Exp. Opin. Ther. Patents, Vol. 5, No. 5, pp. 459-468 (1995)

Lafont, et al. (Lafont), "Which gene for which restenosis?," The Lancet, Vol. 346, pp. 1442-1443 (1995)

Marshall, "Gene Therapy's Growing Pains," Science, Vol. 269, pp. 1050-1055 (1995)

Miller et al. (Miller), "Targeted vectors for gene therapy," FASEB J., Vol. 9, pp. 190-199 (1995)

Orkin et al. (Orkin), "Report and recommendations of the panel to assess the NIH investment in research on gene therapy," pp. 1-41 (NIH, 1995)

GROUNDS OF REJECTION[3]

Claims 8, 10, 11, 13, 15, 18-24 and 25-27 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

We vacate this rejection and remand the application to the examiner for further consideration.

[3] We note that the examiner withdrew (Answer, page 4) the Final Rejection of claims 1,2, 4, 5, 7 and 8 under 35 U.S.C. § 112, first paragraph.

DISCUSSION

New references in the Answer[4]:

We note that the examiner relies on each of these references for the first time in the Answer. As set forth in In re Hoch, 428 F.2d 1341, 1342 n.3, 166 USPQ 406, 407 n.3 (CCPA 1970) "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of the rejection".

Claim construction:

Before considering the rejection under 35 U.S.C. § 112, first paragraph, we must first decide what the claims include within their scope." In re Geerdes, 491 F.2d 1260, 1262, 180 USPQ 789, 791 (CCPA 1974).

The examiner finds (Answer, page 5) "[c]laims 35-55 are broadly drawn to methods of inhibiting tumor growth in vivo or enhancing radiation treatment of a tumor in vitro, by administration of an unspecified adenovirus, which does not comprise a heterologous gene, in combination with a dose of ionizing radiation." [Emphasis added].

In contrast, the examiner finds (Answer, page 4):

> Claims 8, 10, 11, 13, 15, 18-24 and 25-27 are broadly drawn to methods of inhibiting tumor growth in vivo or enhancing radiation treatment of a tumor in vivo, or are drawn to methods of killing tumor cells, implicitly either in vivo or in vitro, by administration of a herpes simplex virus (HSV), which encompass HSV comprising a heterologous

[4] Paper No. 19, mailed April 13, 1998.

> gene, in combination with a dose of ionizing radiation. [Emphasis added].

The examiner notes (Answer, page 9), with reference to the first paragraph on page 6 of the specification, that the methods of claims 8, 10, 11, 13, 15 and 18-27 encompass "HSV vectors comprising heterologous genes expressing therapeutic products that are detrimental to tumor cells, e.g. tumor necrosis factor, cytokines, etc., which is a form of gene therapy."

For their part, appellants argue (Reply Brief, page 4), "this invention does not rely on gene therapy for its effect." Instead, appellants argue (id.) the invention "merely requires the infection of cells in vivo by herpesvirus or adenovirus – something that is known to occur very easily – and treatment using radiation, which also is well established." The specification appears to support appellants' argument. At page 17, the specification discloses "[w]hile these viruses have been used in gene therapy, generally by inserting a therapeutic gene into the HSV-1 viral genome and transfecting into a cell, the present invention does not require the use of specific inserts for function."

However, we note, for example, that originally filed claim 13 required, inter alia, "a virus that contains a DNA molecule comprising a radiation responsive enhancer-promoter operatively linked to an encoding region that encodes a polypeptide having the ability to inhibit growth of a tumor cell." During the course of prosecution, claim 13 was subsequently amended to exclude this limitation. See claim 13 reproduced above. In contrast, claims 40, 41 and 46 (from which claim 51; claims 42-45, 52 and 54; and claims 35-39, 47-50 and 53 respectively

depend) were added during prosecution[5]. Of interest is that each of claims 40, 41 and 46 includes the limitation "lacking an exogenous therapeutic gene."

As set forth in Comark Communications Inc. v Harris Corp., 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (CAFC 1998):

> While we recognize that the doctrine of claim differentiation is not a hard and fast rule of construction, it does create a presumption that each claim in a patent has a different scope. "There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." Tandon Corp. v. United States Int'l Trade Comm'n, 831 F.2d 1017, 1023, 4 USPQ2d 1283, 1288 (Fed. Cir. 1987).

Accordingly, we agree with the examiner, that the scope of claims 8, 10, 11, 13, 15 and 18-27 encompass gene therapy. However, what is unclear from this record is whether the claimed virus is modified at all. We note again, that appellants argue (Reply Brief, page 4), the invention "merely requires the infection of cells in vivo by herpesvirus or adenovirus...." However, with regard to HSV, the specification discloses (bridging paragraph, pages 17-18) "[a]s used in the present invention, the virus, which as been rendered non-pathogenic.... This pharmaceutical composition is then administered in such a way that the mutated virus can be incorporated into cells at an appropriate area" [emphasis added].

We note the examiner recognizes that "[t]he specification discusses preliminary results for the use of certain crippled HSV-1 strains in killing tumor

[5] See Paper No. 9, received April 14, 1997.

cells (page 3, lines 7-25; page 19, lines 5-19). However, there is no discussion on this record with regard to whether the claimed virus is modified, other than by the inclusion of an exogenous therapeutic gene. As set forth in In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989):

> [D]uring patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed. . . . An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.

Enablement:

Notwithstanding the examiner's recognition that the scope of the claims 8, 10, 11, 13, 15, 18-24 and 25-27 encompasses HSV both including and excluding an exogenous gene, the examiner rejected the full scope of the claims based on the unpredictability of gene therapy. See e.g., Answer, pages 7-11. Therefore, it appears that the examiner applied the incorrect legal standard to these claims. If the examiner is concerned that the claims are broad enough to include inoperative embodiments (e.g., gene therapy[6]), we direct the examiner's attention to Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude ... possible inoperative substances...." In re Dinh-Nguyen, 492 F.2d 856, 859-59, 181 USPQ 46, 48 (CCPA 1974)(emphasis omitted). Accord,

[6] We emphasize that we take no position on the merits of the examiner's position that "gene therapy" is unpredictable.

> In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); In re Anderson, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1971). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. *See* e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

On this record, the examiner has made no showing that the number of inoperative combinations effectively forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention.

With regard to the other issues raised by the examiner in rejecting all the claims, the examiner fails to provide factual evidence to support his conclusions and comments. For example, at page 5 of the Answer, the examiner discusses routes of administration and dosages; the examiner raises these issues again at page 13 of the Answer. However, in both instances, the examiner fails to provide evidence to support his position that a person of skill in the art would not be able to determine the appropriate route of administration or the proper dosage. According to appellants (Reply Brief, page 5) "[i]t cannot seriously be argued that providing specific doses for a given route is outside the ability of the skilled artisan to ascertain. As set forth in Hybritech Incorporated v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (1986) cert. denied, 480 U.S. 947 (1987) "a patent need not teach, and preferably omits, what is well known in the art". Without a fact based analysis, the examiner failed to provide the evidence necessary to establish a prima facie case of non-enablement.

The examiner finds (Answer, page 7) that "[i]t is not clear that the mouse model used in the specification would be considered correlatable to the results that the skilled artisan would observe upon practicing the invention in any and all animals, including humans [and] on spontaneous[ly] [occurring] tumors." The examiner finds (id.) "no evidence of record, either in the specification or prior art, to show that results obtained with this model system can be correlated to spontaneous tumor formation from cells of the animal."

In an attempt to meet his burden the examiner relies (Answer, pages 7-9) on Orkin, Lafont and Culver. We note, however, that "gene therapy" is the subject of each of these references. The examiner appreciates this, at least, with respect to Orkin. See Answer, page 8, wherein the examiner finds that "Orkin et al. deals primarily with the unpredictability of gene therapy." Notwithstanding the "gene therapy" focus of each of these references, the examiner finds (id.) that statements in Orkin, and apparently in Lafont and Culver, "are generally applicable to the use of model systems for cancer treatment." The examiner then cites to various sections of these references, where he finds that the authors highlight the inadequacies of animal models. For example, according to the examiner (Answer, pages 8-9) Orkin conclude "that animal models are not satisfactory for studying human disorders"; Lafont teach "[t]he main drawback is related to the discrepancy between striking successes in various animal models and the general failure in human beings"; and Culver "discusses the inadequacies of a rat model for treatment of brain tumors in

humans." The examiner, however, fails to provide the evidence necessary to support his position that the teachings of these "gene therapy" references "are generally applicable to the use of model systems for cancer treatment."

For example, we note that the examiner stops his quotation of Lafont, with the sentence "[t]he main drawback is related to the discrepancy between striking successes in various animal models and the general failure in human beings." However, Lafont go on to discuss these clinical failures. See Lafont, page 1442, column 2. Specifically, Lafont teach (page 1442, first sentence, bridging paragraph, columns 1 and 2) that "[t]he tumoral concept attributes the occurrence of restenosis after angioplasty to the development of neointimal-related smooth-muscle-cell proliferation." In discussing the discrepancy between animal models and humans Lafont explain (page 1442, first sentence, first full paragraph, column 2) that "[t]he remodeling concept differs from the tumoral one because it regards restenosis as independent from neointimal hyperplasia. In animal models, remodelling is a prominent mechanism of restenosis, whereas neointimal hyperplasia is independent of restenosis." In the middle of this same paragraph, Lafont teach that "[t]he remodelling process remains poorly understood and its biological basis is unexplored, so the choice of genes against restenosis is difficult." Lafont therefore, concludes (page 1442, last paragraph, column 2) that "[o]verall, these promising strategies are likely to be successful provided they are targeted against stent-related restenosis. The treatment of restenosis of non-stented arteries requires further research into the mechanisms

of remodelling." Therefore Lafont's conclusion, confirms his statement in the first paragraph of the paper that "a unified genetic approach is unlikely to succeed in all types of restenotic lesion. Existing techniques are aimed at limiting smooth-muscle-cell proliferation – i.e., the antitumoral approach." Thus, from Lafont's discussion it becomes apparent that it is not so much the animal model, as it is the underling genetic basis for the disease. While this may be particularly relevant to "gene therapy," the examiner has not provided the evidence necessary to establish a legal nexus between these "gene therapy" references and the claimed invention, of which the examiner recognizes only claims 8, 10, 11, 13, 15, 18-24 and 25-27 are broad enough to encompass "gene therapy" within their scope.

We remind the examiner as set forth in In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

> "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement."

On reflection, the examiner failed to evaluate the claimed invention under the proper legal standards, and to provide the factual evidence necessary to establish his position. Accordingly, we vacate the rejection of claim 8, 10, 11, 13, 15, 18-24 and 25-27 under 35 U.S.C. § 112, first paragraph and remand the application to the examiner for further consideration.

Upon return of the application, the examiner should take a step back and reevaluate whether the information set forth in the specification in conjunction with the relevant prior art enables one to make and use the claimed invention throughout it scope without undue experimentation. If the examiner finds that a rejection is necessary, the examiner should issue an appropriate Office Action setting forth such a rejection, using the proper legal standards and clearly setting for the facts relied upon in support of such a rejection. In the event such an Office Action is issued, the examiner should provide appellant an appropriate opportunity to respond.

VACATED and REMANDED

DOUGLAS W. ROBINSON)
Administrative Patent Judge)
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)
) BOARD OF PATENT
DONALD E. ADAMS)
Administrative Patent Judge) APPEALS AND
)
) INTERFERENCES
DEMETRA J. MILLS)
Administrative Patent Judge)

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FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TX 78701

DEA/jlb